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REVIEW

Airway and parenchymal manifestations of pulmonary aspergillosis

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Summary
Pulmonary aspergillosis encompasses a heterogeneous group of mycoses that result from either colonisation or pathogenic damage of lung tissue by *Aspergillus* fungi. These clinical entities range from relatively benign saprophytic hypersensitivity associated with fungal inhabitation to life threatening invasive disease. The diagnosis of pulmonary disorders related to *Aspergillus* is on the increase and it is more important than ever those both general and respiratory physicians have a good understanding of these disorders. This paper reviews the contemporary understanding of the clinical, radiographic and histopathological aspects of pulmonary aspergillosis.

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Aspergillus is a ubiquitous genus of moulds, numbering several hundred species.

Only a minority are pathogenic to humans. Overall, *Aspergillus fumigatus* is responsible for 80—90% of cases of pulmonary aspergillosis.[1] Fungal transmission results from the inhalation of tiny airborne conidia which are small enough to reach small peripheral airways. The sinuses and skin provide other potential portals of entry into the body; once breached, haematogenous dissemination places organs such as the central nervous and cardiovascular system at particular risk of infection.

In general, the severity of *Aspergillus* pulmonary disease is directly related to the prevailing fungal burden (influenced by the balance between integrity of host immunity against the virulence of the fungus), the presence and nature of existing lung disease and abnormal bronchial defence mechanisms. The incidence of pulmonary aspergillosis has increased in recent years for a number of reasons including an increased number of susceptible individuals such as organ transplant recipients, a heightened clinical awareness of the disease and improved methods for fungal detection and disease characterization.[1—4] In general, risk factors for developing pulmonary aspergillosis can be divided into: (1) evidence of suppressed immunity (including infection with the human immunodeficiency virus, bone marrow and solid organ transplantation, systemic antibiological therapies, prolonged corticosteroid use, poorly controlled diabetes mellitus and chronic renal failure), (2) presence of structural lung disease (cystic fibrosis, sarcoidosis, chronic obstructive pulmonary disease) and (3) factors that may promote fungal colonisation (wider use of antimicrobials).[1,4,5] The rising incidence of pulmonary aspergillosis coupled with a multitude of disease susceptibility factors means that such cases may increasingly be encountered in outpatient clinics, medical admission departments and the intensive care unit.

Disease manifestations

A. fumigatus is clinically the most important *Aspergillus* species and its manifestations are diverse and sometimes coincident. Traditionally, *Aspergillus* related pulmonary disease has been divided into: *Aspergillus* rhinosinusitis, trachoebronchitis, saprophytic aspergilloma, allergic bronchopulmonary aspergillosis (ABPA), chronic pulmonary aspergillosis and invasive aspergillosis. Although these disease entities appear distinct, airway and parenchymal manifestations of aspergillosis can occasionally co-exist in the same individual.

Airway-centred *Aspergillus* diseases

Aspergillus rhinosinusitis

The frequency of *Aspergillus* nasal and sinus disease in the immune-competent host appears to have increased in recent years, the reasons for which are not entirely clear.[6,7] *Aspergillus* can produce allergic (hypersensitivity) and invasive rhinosinusitis as well as the formation of sinus and parasinus fungal balls that may be mistaken for granulomatous or even malignant disease. Localized allergic *Aspergillus* sinusitis often affects adolescents or young adults with atopy and/or nasal polyposis; production of eosinophil-rich 'peanut butter'-like inspissated material is a frequent complaint and may lead to sinus obstruction.[8,9]

Serum total IgE levels are typically elevated and *Aspergillus* may be cultured from biopsied nasal tissue.[10] Positive *in vivo* (skin testing) and *in vitro* (*Aspergillus*-specific IgE/RAST) responses may also help support the diagnosis of *Aspergillus* rhinosinusitis.[11] The former may be more sensitive than RAST testing in addition to being able to demonstrate delayed cutaneous responses that measurement of circulating IgE does not identify. *Aspergillus*-specific precipitins, typically IgG, may also be elevated in some cases of allergic *Aspergillus* sinusitis. However, elevation of these antibodies, like elevated total IgE, is not required to prove a diagnosis of allergic *Aspergillus* sinusitis.[12] Many patients with *Aspergillus* sinusitis are also clinically and immunologically sensitive to other fungi.

Computed tomography (CT) or magnetic resonance imaging (MRI) may demonstrate obliterated sinuses with hypoattenuated mucosae and focal areas of enhancing material within the opacified spaces[13] Apart from *Aspergillus*, other dematiaceous fungi including *Bipolaris* and *Curvularia* can also cause allergic fungal rhinosinusitis.[14] Treatment with oral corticosteroids following surgical removal of obstructing nasal tissue is advocated in most patients but systemic antifungal treatment has not been shown to be effective.[8] The results of studies using topical anti-fungals are awaited.

Acute fulminant angio-invasive rhinosinusitis due to *A. fumigatus* is characterized by the presence of fungal hyphae within the nasal mucosa and invasion into adjacent vascular and bony structures. Although a relatively rare condition affecting predominantly immune-compromised patients, it is associated with a mortality of up to 80% even with surgical intervention and aggressive systemic antifungal therapy.[15] Chronic granulomatous invasive sinusitis is a distinct form of sinonasal disease found in parts

of Africa and South-east Asia and is caused by infection with *A. flavus* in immune-competent individuals.[13]

Aspergillus tracheobronchitis

Before the term *Aspergillus* tracheobronchitis was adopted in 1926, a number of reports had already documented proximal large airway infection by *Aspergillus* fungi.[16,17] Three different presentations of *Aspergillus* tracheobronchitis were proposed in 1995, based partly on gross morphology: obstructive, ulcerative and pseudomembranous.[18] In practice, these different forms may co-exist. In addition, *Aspergillus* tracheobronchitis may be coexistent with other forms of *Aspergillus*-related pulmonary disease. For example, pseudomembrane formation and subsequent tissue destruction has also been associated with invasive aspergillosis involving the distal lung parenchyma.

Neutropenia and systemic immunosuppression are major risk factors for developing invasive *Aspergillus* tracheobronchitis and account for its increasing frequency among lung transplant recipients and patients with chronic autoimmunediseases, acquired immune deficiency syndrome (AIDS) and malignancy.[19–23] Symptoms may be non-specific and include cough in the majority, exertional dyspnoea, blood-stained sputum, night sweats, fever and wheeze which may be asymmetric.[23,24] Radiographic findings include endo-bronchial soft tissue thickening, obstruction and tracheobronchial stenosis leading to segmental or subsegmental lobar collapse.[23] Bronchoscopic examination and mucosal biopsy is essential for accurate diagnosis. Macroscopic findings include luminal obstruction, mucosal ulceration and exudative pseudomembranes adherent to the underlying mucosa[21] while microscopic demonstration of fungal elements is both sensitive and specific for *Aspergillus* tracheobronchitis and allows a confident diagnosis to be made.[25]

Administration of first-line systemic antifungal agents, particularly voriconazole is recommended by the Infectious Diseases Society of America (IDSA).[1] In lung transplant recipients, early detection of ulcerative *Aspergillus* tracheobronchitis at surveillance bronchoscopy is associated with a more favourable prognosis than the obstructive or pseudomembranous forms.[23,25]

Parenchymal pulmonary aspergillosis

Allergic bronchopulmonary aspergillosis

Allergic bronchopulmonary aspergillosis (ABPA) was first described by Hinson and colleagues in their 1952 report of three patients with fever, wheezing, mucus production, peripheral eosinophilia, pulmonary infiltrates and sputum that cultured *A. fumigatus*.[26] ABPA is a state of hypersensitivity to highly antigenic *A. fumigatus* in atopic immune-competent individuals whose airways are colonised by the fungus. Although previously thought to affect only 1–2% of asthmatics, a recent meta-analysis reported an ABPA prevalence of 12.9% amongst patients attending asthma clinics.[27] Identification of *Aspergillus* in these individuals is important as fungal sensitisation can increase the severity of the underlying asthma.[28] The prevalence of ABPA has been estimated at between 2 and 15% in patients with cystic fibrosis (CF).[29,30]

The hallmark immune abnormality in ABPA is that of an aberrant T-helper cell type 2 (Th2) effector response to *Aspergillus* spores which is mediated by IgE and IgG.[31,32] Immuno-genetic characterization of ABPA has also disclosed human leukocyte antigen (HLA) associations as well as a predisposition to aberrant CD4+ Th2 cytokine induction.[33] In the immediate bronchial environment, the release of such pro-inflammatory cytokines promotes both type I and type III immune responses.[34] The resulting cellular inflammation is in turn exacerbated by repeated exposure to *Aspergillus* antigens. Abnormal muco-ciliary clearance in the bronchi may also play a role in the pathogenesis of ABPA.[31]

The diagnostic criteria for ABPA, initially proposed by Rosenberg and colleagues, have undergone multiple revisions over the past 30 years resulting in the current clinico-radiologic-pathologic approach shown in Table 1.[35] The presence of five criteria is needed to secure a diagnosis of ABPA (Table 1); additional characteristics may strengthen the diagnosis but their absence does not refute it.[36] In the minority of patients without central bronchiectasis, the term ABPA-s has been used to denote seropositive ABPA.[37] This acknowledgement emphasizes the need for clinical vigilance in identifying ABPA to avoid unnecessarily delaying its diagnosis. ABPA-s has also been associated with a milder disease course.[38] The diagnosis of ABPA in the CF population differs in some respects, according to criteria agreed at the 2001 Cystic Fibrosis Foundation conference.[39]

Distinguishing lone asthma from asthma associated with ABPA can be challenging.

Similarly, difficulties may also arise when differentiating exacerbations of CF due to ABPA from ones that are not

Table 1 Diagnostic criteria of ABPA.

Criteria	Essential for ABPA diagnosis?
Asthma	Yes
Total IgE >1000 ng/mL (417 kU/L)	Yes
Elevated serum IgE and/or IgG to *A. fumigatus*	Yes
Immediate cutaneous reactivity to *Aspergillus* species or *A. fumigatus*	Yes
Central bronchiectasis (inner two-thirds of axial lung parenchyma)	Yes to diagnose ABPA-central bronchiectasis If first four criteria have been met, diagnosis is ABPA seropositive (ABPA-s)
Infiltrates seen on chest radiograph	No
Peripheral eosinophilia > 500 mm^3	No
Precipitating antibodies to *A. fumigatus*	No

Adapted from Greenberger, P. A. 2002. Allergic bronchopulmonary aspergillosis. *J Allergy Clin Immunol*. 110(5): 685–92 (31).

Aspergillus-related.[40] It is noteworthy that only a small proportion of the increased total IgE levels measured in ABPA are usually directed against *Aspergillus*.[41] Although total serum IgE levels may useful in monitoring disease, they are subject to fluctuations and do not necessarily predict clinical outcome.[42]

Many of the typical radiological features of ABPA are due to the presence of dilated bronchi with thickened walls. On plain chest radiographs, these abnormalities appear as ring or linear opacities (representing widened bronchi seen *en face* and in the coronal plane respectively) and have a predilection for the upper and central regions of the lungs. Signs indicating endobronchial impaction by inspissated mucus and fungal debris such as transient bronchocentric opacities, lobar collapse and small peripheral lung nodules may also be present.[43] Fibrotic scarring, when evident, is more likely to occur in the upper lung zones. CT features of ABPA include central airway dilatation due to varicose or cystic bronchiectasis, exudative bronchiolitis (tree-in-glove opacities) and tubular 'finger in glove' shadows of dilated, impacted bronchi.[44] In a few cases, this is so marked as to produce the 'hyperdense bronchial mucous plugging sign' (Fig. 1).[45]

A clinical staging classification that takes into consideration the typical relapsing-remitting nature of ABPA is also in use.[46] In reality, most patients do not progress predictably through the different stages of disease although recognition of the specific features of each stage aids clinical phenotyping. Stages I (acute) and III (exacerbation) represent the most symptomatic stages and are characterized by, amongst others, marked elevations in serum IgE and inflammatory radiographic opacities. At times of clinical remission (stage II), these changes may abate and a state of complete remission may become evident.[31] Stage IV describes a state of glucocorticoid-dependence to achieve either clinical or serological control while stage V ('end-stage') is accompanied by established lung damage such as fibrosis and/or extensive bronchiectasis. These patients remain susceptible to clinical exacerbations.

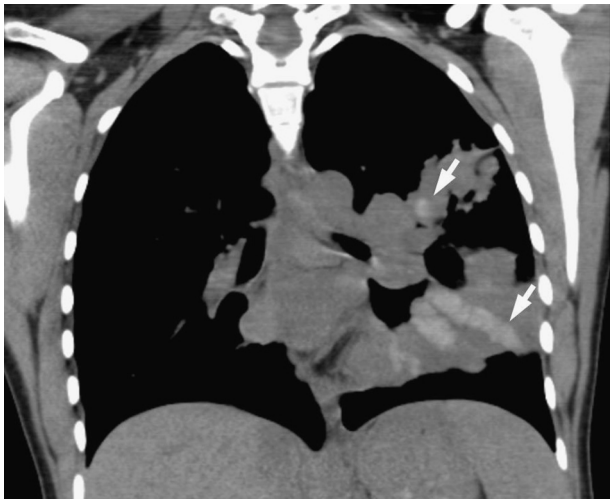

Figure 1 Coronal CT image of a patient with allergic bronchopulmonary aspergillosis (ABPA) demonstrating the hyperdense mucus sign. Arrows highlight high attenuation mucoid impaction within abnormally dilated bronchi.

Pharmacological management of ABPA is aimed at controlling the host immunological response to *Aspergillus* antigens and minimising the fungal antigen load within the airways.[46] In addition to corticosteroids as the mainstay of immune-modulatory therapy, itraconazole has emerged as the antifungal drug of choice.[47] Its short-term efficacy in decreasing circulating IgE levels and inducing a steroid-sparing effect has been demonstrated in two randomized controlled trials.[48] However, lasting benefit beyond the 16 weeks assessed in both studies has been difficult to demonstrate. The optimum time for commencing itraconazole therapy remains unclear; practical guidelines suggest a trial in those who have experienced a first exacerbation on corticosteroids or those who remain symptomatically steroid-dependent.[31] Early antifungal treatment with itraconazole has also been advocated in the prevention of fibrotic lung sequelae.[1,38] Experience with other antifungal agents such as voriconazole and nebulized amphotericin B has been more limited.[49,50] Despite their widespread use, the precise role of inhaled corticosteroids in standard care of ABPA remains incompletely understood. More recently, reports of the use of recombinant anti-IgE antibody in ABPA have been published.[51,52]

Aspergilloma

An aspergilloma is a localised mass of *Aspergillus* elements and cellular debris which has a low potential for tissue invasion due to its saprophytic nature. It most commonly develops in a pre-existing lung cavity arising from past tuberculosis, fibrobullous sarcoidosis, bronchiectasis, ankylosing spondylitis or a pneumatocele and may lie quiescent for years.[43,53] Multiple aspergillomata may occasionally develop and may be difficult to distinguish from chronic cavitary aspergillosis. The most common symptom from aspergilloma is haemoptysis which is typically mild but has a tendency to become severe or even life-threatening.[54] The source of bleeding may arise from bronchial arteries or anastomotic communications between pulmonary and bronchial arteries associated with the aspergilloma.[55] Although unusual, aspergillomas may also undergo spontaneous shrinkage or disappear.[56,57]

On plain chest radiography, an aspergilloma typically appears as an ovoid or round opacity located within a lung cavity. Localised pleural thickening may occasionally be apparent although this sign is best appreciated on CT.[58] Separation of the fungal mass from its surrounding cavity wall may be accentuated by a crescent of air around the mycetoma known as the Monod sign which is not to be confused with the 'air crescent sign' described in invasive aspergillosis. Positional changes of the intra-cavitary mass during imaging may indicate its mobility within the cavity. Occasionally, a broncho-cavitary connection may be identified (Fig. 2). Examination of sputum, bronchoalveolar lavage (BAL) fluid and surgically resected material may reveal the presence of *Aspergillus* hyphae.[57] Often, elevated titres of serum *Aspergillus*-specific IgG precipitins are also detected, particularly in corticosteroid-naïve patients.[59]

The optimal treatment for indolent or mildly symptomatic aspergilloma is unknown.

Systemic antifungal therapy does not effectively alter the disease course due to poor drug penetration into

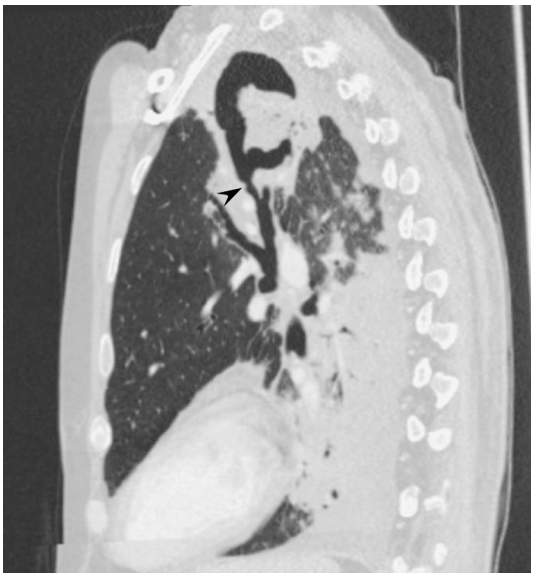

Figure 2 Sagittal CT image of a patient with solitary left upper lobe aspergilloma and left lower lobe consolidation. A broncho-cavitary communication is apparent (arrowhead).

mycetomal cavities.[59,60] In this regard, drugs of the triazole group may be more effective than amphotericin B.[1] Intra-cavitary instillation of anti-mycotics has previously been used with variable clinical response.[61,62] Although increasingly available, selective embolization of bronchial and nonbronchial arteries offers only a temporizing effect until surgical treatment can be undertaken.[63]

Since the first surgical removal of aspergilloma in 1947, experience with operative treatment has continued to grow. Fig. 3 shows the gross pathology of a resected aspergilloma within a lung cavity caused by sarcoidosis. It is widely acknowledged that only surgery can offer definitive treatment for this condition, provided that cases are appropriately selected.[64–66] Surgical complications may be substantial and include intra-operative haemorrhage, persistent air leaks and infection of the residual space. At times, it may be necessary to remove a greater quantity of lung than was preoperatively anticipated. In a retrospective analysis of 72 cases, 10-year cumulative survival did not differ between patients undergoing surgery and adjuvant anti-fungal therapy (74.8%) versus those who only received surgery (78.9%).[67] The optimal timing for commencing anti-fungal agents in such setting remains unclear.

Figure 3 Pneumonectomy specimen containing aspergilloma in the apex of the left lower lobe. Hemorrhagic changes in the lung parenchyma clearly demonstrated.

Chronic pulmonary aspergillosis (necrotising and cavitary)

The classification of chronic aspergillosis is complicated by the existence of overlapping clinico-radiologic phenotypes that may follow variable clinical courses.

Chronic necrotising pulmonary aspergillosis (CPNA), most commonly encountered in individuals with chronic or debilitating systemic illnesses, is one such example (Fig. 4). Although it has the potential to cause lung tissue destruction, CPNA may remain indolent for long periods of time without producing vascular invasion.[68] The main differential diagnosis for CNPA is chronic cavitary pulmonary aspergillosis (CCPA), a disease notable for the formation of multiple pulmonary cavities that do not invariably contain fungal masses.[69] Such cavities may result from direct fungal infiltration of lung parenchyma although CCPA can also develop in existing tuberculous fibro-cavitatory spaces.[69] Regardless of the specific type of chronic aspergillosis, the ensuing lung damage may predispose to the development of broncho-pleural fistulae.[70] IgG precipitating antibodies against *Aspergillus* antigens are positive in the majority of affected patients and successful culture of *Aspergillus* in sputum or BAL fluid, or histological confirmation of fungal invasion help to establish the diagnosis.

The mainstay of treatment for both these conditions is high dose systemic antifungal therapy. In recent years, the use of oral triazole compounds such as itraconazole and voriconazole has overtaken the role of amphotericin B which is now largely reserved for severe disease.[71,72] However, the optimal duration of treatment for chronic pulmonary aspergillosis remains unclear. In one recent study of immune-

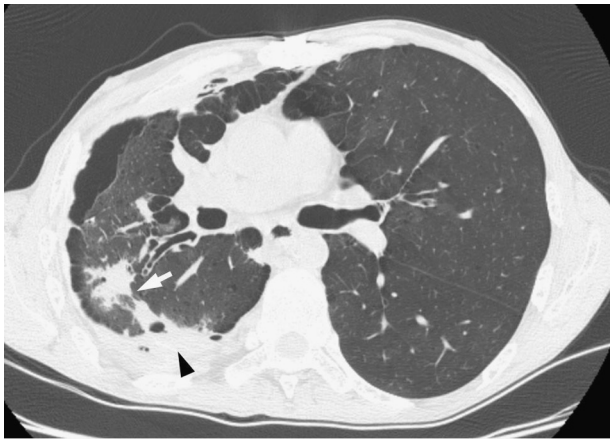

Figure 4 Axial CT image illustrating features of chronic pulmonary necrotizing aspergillosis (CPNA) including consolidative opacities, areas of cystic change and pleural thickening (arrowhead). Limited adjacent ground-glass attenuation is not uncommonly observed, denoting tissue damage with focal haemorrhage.

competent individuals, the mean duration of treatment was 6.5 months (range 4—36 months).[72] Radiological improvement and fungal eradication were attained in 58% of those who completed follow-up. Success with adjunctive administration of interferon-gamma 1b has also increased interest in the role of 'immune enhancers' to boost the efficacy of anti-fungal drugs.[73,74] Surgical intervention for chronic pulmonary aspergillosis is rarely undertaken due to the high risk of complications and the high level of co-morbidity in affected individuals.

Invasive pulmonary aspergillosis

Invasive pulmonary aspergillosis (IPA) is almost exclusively a disease of compromised immunity such as that encountered in transplant recipients (bone marrow and lung), those with haematological malignancies, prolonged neutropenia, AIDS, chronic corticosteroid treatment or cytotoxic therapy.[56] Beyond these classic groups, it is increasingly appreciated that other risk factors for IPA include anti-tumour necrosis factor therapy, prolonged critical illness, severe COPD and cardiothoracic and vascular surgery are increasingly appreciated (see Table 2).[75—87] In clinical series, between 5 and 10% of haematopoietic stem cell transplant (HSCT) recipients develop IPA, mostly within the first few months of their transplant, and face a mortality rate that exceeds 80%.[88,89] For these patients, the presence of graft-versus-host disease (GvHD), iatrogenic immunosuppression and prolonged or severe neutropenia are major predisposing factors to IPA.[90] Overall, an underlying risk factor is not clearly defined in around 2% of cases.[91] In one review of patients on a mixed medical-surgical ICU, risk factors for developing IPA were categorized as high, intermediate and low, and included determinants as diverse as severe neutropenia to post-cardiac surgery status.[86]

Microbiologic analysis for IPA by routine methods is challenging; up to 70% of immuno-compromised patients with confirmed IPA may have a negative sputum culture.[92] Serum and BAL fluid measurement of galactomannan (Gm), a polysaccharide fungal cell wall component, allows *Aspergillus* antigenaemia to be detected and quantified.[93] The sensitivity and specificity of assaying Gm in different at-risk populations is presently being evaluated; in the critical care setting, the diagnostic utility of Gm in BAL fluid has shown early promise although false positive results may occur in patients taking beta-lactam antibiotics.[78,94] Serum assays of other *Aspergillus* antigens such as β-glucan are currently in development.[95]

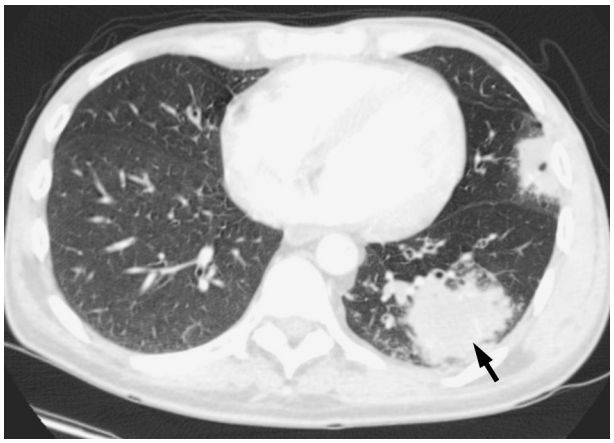

Figure 5 Axial CT image showing a large subpleural 'target lesion' in the left lower lobe (arrow) and a smaller nodule in the lingula in a patient with invasive pulmonary aspergillosis (IPA). Such macronodules typically have a rim of ground-glass opacity (the halo sign) representing haemorrhage and vascular invasion.

The most consistent radiologic finding in IPA is that of one or more pulmonary macronodules typically surrounded by a halo of ground-glass opacity, the latter representing perilesional haemorrhage associated with alveolar invasion.[43,44] An example is shown if Fig. 5. Depending on the stage of IPA, other radiologic features may include the air crescent sign (denoting infarction and retraction of the mycotic nodule) and pneumonic consolidation. It should be noted that the former is also encountered in other fungal infections such as pulmonary mucormycosis.[96] However, its relatively late appearance after the acute phase of IPA limits the value of

Table 2 Risk factors for developing invasive aspergillosis in the ICU categorised by likelihood of risk.

High risk	Intermediate risk	Low risk
Neutropenia ($<$500neutrophils/mm^3)	Prolonged treatment with corticosteroids before admission to the ICU	Severe burns
Haematological malignancy	Autologous bone marrow transplantation	Other solid-organ transplant recipients (e.g., heart, kidney, or liver transplant recipients)
Allogeneic bone marrow transplantation	Chronic obstructive pulmonary disease	Steroid treatment with a duration of 7 days
	Liver cirrhosis with a duration of stay in the ICU 17 days	Prolonged stay in the ICU (121 days)
	Solid-organ cancer	Malnutrition
	HIV infection	Post-cardiac surgery status
	Lung transplantation	
	Systemic diseases requiring immunosuppressive therapy	

Adapted from Meerseman et al. 2007.[86]

the air crescent sign as an early marker of disease. It is occasionally preceded by the appearance of another abnormality, the hypodense sign of necrotic lung infarction.[97] While the appearance of focal hypo-intensity is not limited to IPA *per se*, its presence in the correct clinical setting may strongly suggest *Aspergillus* lung invasion. More recently, the reverse halo sign has also been described in invasive fungal infections although it is more commonly associated with organising pneumonia.[98] Its sensitivity for identifying IPA remains to be tested in a larger number of cases. Pleural effusions are unusual in IPA.[99]

The diagnosis of IPA can be challenging. To help weigh the confidence of diagnosis of this and other fungal infections, a joint group of the European Organisation for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) produced criteria (later revised) for defining the likelihood of invasive fungal infection (Table 3).[100,101] According to these criteria, *proven* IPA requires the histopathologic or direct microscopic demonstration of *Aspergillus* elements in tissue from patients highly suspected as having the disease. A diagnosis of *probable* IPA requires the presence of a predisposing host factor along with clinical and mycological evidence of invasive fungal disease. In this category, mycological criteria also include indirect tests such as quantification of Galactomannan in body fluids. *Possible* IPA cases relate to those where appropriate host factors and clinical evidence of IPA may be present but are not ultimately accompanied by mycological evidence. More recently, a clinical algorithm based on satisfying 4 criteria incorporating *Aspergillus* culture from the respiratory tract, compatible clinical findings,

Table 3 Revised ETORC/MSG criteria for the diagnosis of IPA.

Criteria	Proven	Probable	Possible
Histological evidence • Microscopic analysis of sterile material — Histopathologic, cytopathologic or direct microscopic examination of a specime obtained by needle aspiration or biopsy in which hyphae or melanised yeast like forms are seen accompanied by evidence of associated tissue damage • Culture of sterile material — Recovery of mould or "black yeast" by culture of a specimen obtained by sterile procedure form normally sterile and clinically or radiologically abnormal site consistent with an infectious disease process, excluding broncho-alveolar lavage fluid, a cranial sinus cavity specimen and urine	Required	Absent/ not available	Absent/ not available
Host factors • Recent history of neutropenia ($<0.5 \times 109$ neutrophils/L) for >10 days temporarily related to onset of fungal disease • Receipt of allogenic stem cell transplant • Prolonged use of corticosteroids (excluding patients with ABPA) at a mean dose of 0.3 mg/kg/day of prednisolone for >3 weeks • Treatment with either recognised T cell immunosuppressants, such as cyclosporine, TNF-α blockers, specific monoclonal antibodies (such as laemtuzamab), or nucleoside analogues during the past 90 days • Inherited severe immune deficiency (such as chronic granulomatous disease or severe combined immunodeficiency)	Not required	Required	Required
Clinical criteria • Lower respiratory tract fungal disease with the presence on CT of one or more of (1) dense, well circumscribed lesion(s) with or without halo sign (2) air crescent sign (3) cavity • Tracheobronchitis • Sino-nasal infection • CNS infection	Not required	Required	Required
Mycological Criteria • Direct test (cytology, direct microscopy or culture) • Indirect test 1) Galactomannan antigen in plasma, serum, bronchoalevlar fluid or CSF) or 2) β D-glucan detected in serum	Not required	Required	Absent

Adapted from Pauw, Walsh et al. 2008.[101]

suggestive radiological abnormalities and a host predisposing factor (such as neutropenia).[87]

IPA is associated with a very high mortality even when empiric treatment is initiated early.[102] Treatment failure is common when it is administered late or to patients who are profoundly neutropenic or have disseminated disease.[91,94] Of the triazole-based agents, voriconazole is widely recommended as first line treatment for IPA due to its superior efficacy over amphotericin B and its additional actions against *Aspergillus terreus*.[1,103–105] There is increasing evidence that therapeutic drug monitoring (TDM) of voriconazole may improve treatment endpoints. Unwanted and at times severe adverse effects as well as treatment inefficacy occur as a result of unpredictable variations in circulating voriconazole levels. In one study of over 50 adult patients on this drug, voriconzole TDM improved both treatment success and safety.[106] In a more recent randomized study of 110 patients with invasive fungal infections, patients assigned TDM were found to develop fewer adverse drug events and experience a higher rate of partial or complete treatment response.[107] However, the usefulness of TDM of voriconazole has failed to be shown in other studies. Plasma trough concentrations were found to correlate poorly with drug dose and treatment response in immunocompromised pediatric patients with invasive fungal disease.[22] In the adult population, a large retrospective multi-center study that evaluated 264 patients receiving voriconazole as targeted or pre-emptive treatment of IPA failed to find a correlation between its concentration and treatment outcome.[108]

Combination therapy with different anti-fungals is used when disease progression occurs on single-agent treatment. However, the potential for adverse drug interactions with poly-pharmacy should borne in mind and the role of combination antifungal therapy in aspergillosis as either initial or salvage therapy remains unproven. Combination therapy is not recommended in current practice guidelines. Posaconazole and caspofungin have been shown to be effective in refractory cases of invasive aspergillosis.[109,110] In addition, Caspofungin has been shown to be efficacious as salvage therapy in patients intolerant of or resistant to standard anti-fungal treatment.[1] A randomised trial comparing voriconazole with or without anidulafungin is currently underway.[111] In individuals at high risk of IPA, a role for prophylactic posaconazole has been suggested (1). Encouraging results with immune augmentation strategies using myeloid colony stimulating factors (G-CSF or GMCSF) and recombinant interferon-gamma (IFN experience in this field remains relatively limited.[1,112,113] A successful outcome following surgical intervention of IPA has also been previously reported but this approach, for obvious reasons, is unsuitable for most patients.[114,115]

Summary

The apparent frequency of pulmonary aspergillosis has risen as a result of greater clinical awareness, improved detection and perhaps most significantly, an increasing number of at-risk individuals. Susceptibility to aspergillosis is not confined to those with classical risk factors such as neutropenia and allogeneic organ transplant. It is increasingly recognized that susceptible patients also include those requiring organ support on critical care units, those affected by malignancies, chronic debilitating conditions, granulomatous lung disorders and iatrogenic immunosuppression related to the use of anti-biologic agents. The development of new diagnostic laboratory tests is expected to meet demands for increasingly sophisticated ways to prove *Aspergillus* pathogenicity. More accurate radiological characterization of fungus-associated airway and lung damage will broaden the role of CT as a crucial diagnostic tool. Although medical treatment of pulmonary aspergillosis as a whole remains challenging, an increasing number of pharmacological agents are now available to the treating clinician. In recent years, realization that susceptibility to specific forms of this disease is inherently influenced by a dysfunctional host defence system has led to the use of immune-modulatory strategies such as anti-IgE antibodies (for ABPA) and recombinant interferon-gamma therapy (for chronic necrotizing and invasive aspergillosis). Much hope has also been placed on the application of functional genomics to identify *Aspergillus* targets against which antifungal agents will exert greater activity. Failure to control the clinical burden wrought by *Aspergillus* fungi will inevitably mean a disproportionately higher death toll amongst relatively select groups of vulnerable individuals.

Conflict of interest statement

None.

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